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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,797	07/23/2001	Jacques Diaz	3806.0510-00	2702

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Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,797	DIAZ ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-46 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,7-17,21-24,26-36 and 38-46 is/are rejected.

7)☒ Claim(s) 6,18-20,25 and 37 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

Claim 2 is objected to because of the following informalities: The word 'heparin' is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

Claims 44-46 are drawn to a method of treating a patient comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 2, 10 and 26 is an active ingredient present in an amount efficacious for such treatment.

Claims 44-46 are missing the critical element. Claims 44-46 recite a method of treating a patient, but do not recite what condition is being treated by the instantly claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-17, 21-24, 26-36, 38-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mardiguian (AU-B-70519/81) in combination with Mardiguian (USPN 6,384,021), Mardiguian (USPN 4,440,926), Galezowski et al (Journal of Chemical Society, Faraday Transactions 1997, 93(15), 2515-2518) and Weitz et al (USPN 6,075,013).

Claims 1-5, 7-17, 21-24, 26-36, 38-46 are drawn to a composition comprising at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin having a mean molecular weight in the range of 1500-3000 daltons, an anti-Xa activity in the range from 94-150 IU/mg, an anti-IIa activity in the range up to 10 IU/mg and a ratio of anti-Xa : anti-Iia activity og greater than 10:1; wherein the sulphated polysaccharide of heparin has 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate at at least one end; the alkaline-earth metal salt is sodium, potassium, calcium or magnesium; a composition having an anti-Xa:anti-IIa activity of greater than 25; a method of preparing alkali or alkaline-earth metal salt of a sulphated polysaccharide of heparin by depolymerization of the quaternary ammonium slat of the benzyl ester of heparin with a base having a pKa greater than 20, converting the depolymerized heparin to a sodium salt, saponifying the ester and optionally purifying the product with hydrogen peroxide; depolymerizing heparin with different bases and a method of treating venous thrombosis by administering the said composition to a patient.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Mardiguian (AU-B-70519/81) teaches (see Complete Specification, page 5, line 21 through page 6, line 11) mixtures of sulphated polysaccharides of heparin having a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at one end of the chain having 3-20 units and in the free form or salt form particularly a sodium, calcium or magnesium salt. Example 1 (page 14, line 23) teaches the preparation of sulphated polysaccharide of heparin by first converting benzethonium heparinate into the benzyl ester and then to the corresponding sodium salt by treatment with sodium acetate and methanol. The sodium salt is then treated with aqueous sodium hydroxide to effect the depolymerization and saponification to yield the sodium salt of heparin.). The depolymerization of benzethonium salt of the benzyl ester of heparin is also taught by Mardiguian (AU-B-70519/81, see page 23, Example 18, line 21-page 24, line 21). The pKa of 1,5-diaza-bicyclo [4.3.0] non-5-ene is 23.4 (see Galezowski et al, Abstract, Journal of Chemical Society, Faraday Transactions 1997, 93(15), 2515-2518). The product of Example 1 also exerted an anti-Xa effect much more intense that of commercial heparin (see page 29, below Table D)

However, Mardiguian (AU-B-70519/81) does not teach heparin with a mean molecular weight in the range of 1500-3000 daltons, with an anti-Xa activity in the range from 94-150 IU/mg and an anti-IIa activity in the range up to 10 IU/mg, a ratio of anti-Xa : anti-IIa of greater than 10:1; purification using hydrogen peroxide, a mole ratio of the base to the quaternary ammonium salt of the benzyl ester of heparin from 0.2:1 to 5:1 and degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin in the range from 50 to 100%.

Mardiguian (USPN 6,384,021) realized the need for very low molecular weight heparins especially in the range of 2000-4000 daltons due to their selective action on activated factor X and hence the need for a selective depolymerization technique. Mardiguian teaches (col. 3, example 1- example 5) selective depolymerization of the ammonium salt of heparin via beta elimination. This method of Mardiguian provided (columns 5 and 6) compositions of low molecular weight heparins containing 4,5-unsaturated glucuronic acid 2-O-sulphate at one end and containing 1 to 12 saccharide units. The mean molecular weights are in the range 2000-4000 and the anti-Xa activity in the range of from 100-120 IU/mg and anti-IIa activity in the range up to 8 IU/mg (see Analysis of the Products, col. 5). The anti-Xa : anti-IIa ratio is also greater than 10:1 and 25:1 (see col. 5, Analysis of the Product). The compositions are also useful as anti-thrombic medicaments (see col. 2, lines 28-30 and col.6, claims 5-7).

Mardiguian (USPN 6,384,021) does not teach the purification of heparin using hydrogen peroxide; the use of a mole ratio of the base to the quaternary ammonium salt of the benzyl ester of heparin from 0.2:1 to 5:1 and degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin in the range from 50 to 100%.

Mardiguian (USPN 4,440,926) teaches esterification of benzethonium salt of heparin

using different substituted benzyl chlorides and subsequent conversion of these to sodium salts using sodium acetate in methanol (see example 1, col. 5 and example 4, col. 6). Esterification range is 10-90% (see abstract). Mardiguian also reports (see col. 4, line 67 - col. 5, line 8) that the compounds of his invention undergo depolymerization when subjected to the action of a base such as sodium hydroxide or an organic base such as 1,5-diaza-bicyclo [4.3.0] non-5-ene.

However, Mardiguian (USPN 4,440,926) and the other art cited above do not teach in general a purification step after depolymerization or purification of heparin using hydrogen peroxide; the use of a mole ratio of the base to the quaternary ammonium salt of the benzyl ester of heparin from 0.2:1 to 5:1.

Weitz et al (USPN 6,075,013) teach (see col. 9, line 64-col. 10, line 13) the use of ultrafiltration for the separation of low molecular weight heparins. This can be included as an additional step in the preparation of very low molecular weight heparins.

It is obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings given above and come up with a method of producing low molecular weight heparin as instantly claimed with reasonable amount of success. All the necessary steps to produce low molecular weight salt of sulphated polysaccharide of heparin seems to be set forth in the prior art cited above.

The teachings can be combined to produce compositions comprising at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin:

1. With a mean molecular weight range of 1500-3000 with anti-Xa activity in the range from 94-150 IU/mg and anti-IIa activity in the range of up to 10 IU/mg.

2. Containing sulphated polysaccharide from 2 to 26 units and having 4,5-unsaturated glucuronic acid 2-O-sulphate unit at least on one end.

3. Carry out the depolymerization of the quaternary ammonium salt of the benzyl ester of heparin in an organic medium by using a different nitrogen-containing base (with pKa greater than 20 or even less than 20), which is structurally similar to 1,5-diaza-bicyclo [4.3.0] non-5-ene.

4. Adjust the mole ratio of base to quaternary ammonium salt to an optimum value.

5. Use saponification as a separate step.

6. Optimize the degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin and

7. Use the instantly claimed compositions for treating venous and arterial thrombosis and thrombotic accidents.

An artisan with ordinary skill in the art would be motivated to do so because the reagents and conditions used are mild and lead to the desired degree of polymerization and yield a product which has an optimum composition, regulated by operating conditions, according to average molecular weight desired.

Claims 6, 18, 19, 20, 25, and 37 are objected to since these claims depend on independent claims that have been rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 703-305-4837. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

GK
July 29, 2002

JAMES O. WILSON
PRIMARY EXAMINER
GROUP 1600